SPECIFICATION AND CLAIM OBJECTIONS

In the Office Action dated March 8, 2002, the specification is objected to for reciting "Salmonella" without italics. Furthermore, the specification is objected to for use of worldwide web addresses. In addition, claim 5 is objected to for a typographical error in reciting "Enterobacteriaceae".

As an initial matter, Applicants wish to thank the Examiner for identifying recitation of genus and species names without italics and for typographical errors. Applicants have reviewed the specification and claims, and have hereby corrected, as set forth above, these inadvertent errors. Accordingly, Applicants request that these objections be withdrawn because they have been obviated.

With regard to the worldwide web (URL) addresses, Applicants respectfully submit that a URL address may be included in a specification. According to MPEP §608.01, the specification may not have a hyperlink or a browser-executable code, which are defined as a URL placed between these symbols "< >" and http:// followed by a URL address. In this case, Applicants respectfully submit that the instant application recites URL addresses only and, therefore, will not appear as an active link. Accordingly, Applicants respectfully submit that this objection has been obviated and request that it be withdrawn.

REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

In the Office Action, claims 18, 25, 34, 44, 51, and 52 were rejected under 35 U.S.C. §112, second paragraph as indefinite. In addition, claims 3-8, 19-21, and 26-28 were also rejected under 35 U.S.C. §112, second paragraph as indefinite. Applicants respectfully submit that these grounds of rejection have been rendered moot because claims 3-8, 18-21, 25-28, 34, 44, 51, and 52 have been cancelled. Accordingly, Applicants request that these rejections be withdrawn.

REJECTION UNDER 35 U.S.C. §102(b)

In the Office Action, claims 1-14, 19-21 and 26-28 were rejected under 35 U.S.C. §102(b) as unpatentable over WO 94/25598 (Kay *et al.*). In particular, it is alleged

that Kay *et al.* teach *agfA* genes of *Salmonella* that have been engineered to contain foreign DNA encoding an epitope or antigen. It is further asserted that Kay *et al.* teach that the bacterial host cell that comprises the recombinant gene is able to express a stable *Salmonella* AgfA fimbrin protein fused to one or more foreign antigens. In addition, Applicants are assertedly required to show that the recombinant gene of the prior art does not possess the same material structural and functional characteristics of the claimed recombinant gene because the Office does not have the facilities to examine and compare Applicants' recombinant gene with the prior art recombinant gene.

Applicants respectfully traverse this ground of rejection and submit that Kay *et al.* fail to meet every limitation of the instant claims and, therefore, fail to anticipate the claimed invention. As described in the specification (*see, e.g.*, at page 2, lines 13-23) and recited in the claims, the present invention is directed to, in pertinent part, to a recombinant nucleic acid molecule that encodes a chimeric AgfA fimbrin polypeptide comprising at least one heterologous antigen, wherein said chimeric polypeptide comprises an AgfA fimbrin amino acid sequence as set forth in SEQ ID NO:5 or a homologue thereof in which at least one fimbrin polypeptide segment that is present in either SEQ ID NO:5 or the homologue thereof is replaced with a heterologous polypeptide antigen segment that is equal in length to the fimbrin polypeptide segment. In another aspect, the invention is directed to, in pertinent part, to a host cell that contains and expresses a recombinant nucleic acid molecule to produce a chimeric fimbrin polypeptide as set forth above and, further, produces stable fimbriae comprising the chimeric fimbrin polypeptide of the instant invention. As discussed in greater detail below, Applicants respectfully submit that Kay *et al.* fail to teach or suggest an AgfA fimbrin amino acid sequence in which at least one fimbrin polypeptide segment is replaced with a heterologous polypeptide antigen segment and that such a chimeric fimbrin polypeptide can assemble to form stable fimbriae.

Kay *et al.* merely describe how to make attenuated *Salmonella* strains having a mutated *agfA* gene. For example, Kay *et al.* provide a *Salmonella* strain having the *agfA* gene insertionally inactivated by a antibiotic (chloramphenicol) resistance gene, which only truncates the *agfA* message and does not result in an AgfA protein having foreign antigen or epitope (*see* Kay *et al.* at page 40, Example 12). Although Kay *et al.* mention that a fimbrin protein may be

fused to a foreign antigen to elicit an immune response, no such fusion polypeptide to elicit an immune response is described. The closest example provided by Kay *et al.* is an AgfA protein *fused* to the enzyme alkaline phosphatase (PhoA), wherein the enzyme is used as a marker to detect the mutated AgfA (*see* Kay *et al.* at page 29, Example 3). Therefore, Kay *et al.*, while describing an *agfA* gene mutated by insertional inactivation or by protein fusion, fail to teach or suggest a chimeric polypeptide comprising an AgfA fimbrin amino acid sequence as set forth in SEQ ID NO:5 or a homologue thereof in which at least one fimbrin polypeptide segment that is present in either SEQ ID NO:5 or the homologue thereof is *replaced* with a heterologous polypeptide antigen segment that is equal in length to the fimbrin polypeptide segment.

Furthermore, Kay *et al.* fail to teach chimeric polypeptides according to the instant invention that assemble to form stable fimbriae. Again, Kay *et al.* mention that an attenuated *Salmonella* strain having fimbriae with a foreign antigen may be made, but fail to teach how to make such an embodiment. Furthermore, neither the insertionally inactivated fimbrin genes or fimbrin-PhoA fusions resulted in *Salmonella* having fimbriae, much less having fimbriae comprising a chimeric fimbrin polypeptide according to the instant invention. Therefore, Applicants submit that Kay *et al.* fail to provide every element of the instant claims.

Accordingly, Applicants respectfully submit that the instant claims distinguish patentably over Kay *et al.* and, therefore, satisfy the requirements of 35 U.S.C. §102(b). Hence, Applicants request that this rejection be withdrawn.

REJECTION UNDER U.S.C. §103(a)

In the Office Action, claims 18, 25, 34, 44 and 51 were rejected under 35 U.S.C. §103(a) as unpatentable over WO 94/25598 (Kay *et al.*) in view of Collinson *et al.* (*J. Bacteriol. 178*:662-667, 1996). More specifically, it is asserted that it would have been obvious for a person having ordinary skill in the art to replace the recombinant *agfA* gene taught by Kay *et al.* with an *agfA* homolog, such as *csgA*, provided by Collinson *et al.* to produce a stable recombinant fimbrin protein according to the instant invention.

Applicants respectfully traverse this ground of rejection and submit that Kay *et al.* and Collinson *et al.*, taken alone or in combination, fail to teach or suggest the claimed invention and, further, would not have motivated a person having ordinary skill in the art to arrive at the

claimed invention with a reasonable expectation of success. The present invention is directed to, in pertinent part, to a recombinant nucleic acid molecule that encodes a chimeric AgfA fimbrin polypeptide comprising at least one heterologous antigen, wherein said chimeric polypeptide comprises an AgfA fimbrin amino acid sequence as set forth in SEQ ID NO:5 or a homologue thereof in which at least one fimbrin polypeptide segment that is present in either SEQ ID NO:5 or the homologue thereof is replaced with a heterologous polypeptide antigen segment that is equal in length to the fimbrin polypeptide segment. As set forth above, Kay *et al.* fail to teach or suggest an AgfA fimbrin amino acid sequence in which at least one fimbrin polypeptide segment is *replaced* with a heterologous polypeptide antigen segment, as provided by the instant invention. Furthermore, as set forth in the Office Action, Kay *et al.* concededly fail to teach or suggest a homologue of the *agfA* gene.

Applicants respectfully submit that the disclosure of Collinson *et al.* fails to remedy the deficiencies of Kay *et al.* and, therefore, the combination of Collinson *et al.* with Kay *et al.* fails to teach or suggest the instant invention. Collinson *et al.* merely characterize the *Salmonella afgBAC* operon and compare this to the homologous *E. coli csgBA* region. In fact, Collinson *et al.* are silent with regard to a recombinant nucleic acid molecule that encodes a chimeric polypeptide comprising AgfA or homologue thereof and at least one heterologous antigen as provided by the instant invention. Therefore, Collinson *et al.* provide a suggestion or motivation for a person having ordinary skill in the art to combine Collinson *et al.* with Kay *et al.* Applicant respectfully submits that the mere fact that the teachings of the prior art *can* be combined or modified, or that a person having ordinary skill in the art is *capable* of combining or modifying the teachings of the prior art, does not make the resultant combination *prima facie* obvious, as the prior art must also suggest the desirability of the combination (*see, e.g.*, *In re Mills*, 16 USPQ2d 1430, Fed. Cir., 1990; *In re Fritch*, 23 USPQ2d 1780, Fed. Cir., 1992).

Hence, Applicants respectfully submit that the Office Action has not set forth a *prima facie* case of obviousness, where the cited references fail to teach every limitation of the instant invention and fail to provide motivation for a person having ordinary skill in the art to modify or combine the prior art teachings to arrive at the claimed invention with a reasonable expectation of success. Accordingly, Applicants respectfully submit that the instant claims

distinguish patentably over Kay *et al.* and Collinson *et al.* and, therefore, satisfy the requirements of 35 U.S.C. § 103(a). Applicants request that this rejection be withdrawn.

All of the claims pending in the application (claims 56-74) are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. The Examiner is urged to contact the undersigned attorney if there are any questions prior to allowance of this matter.

Respectfully submitted,

Seed Intellectual Property Law Group PLLC

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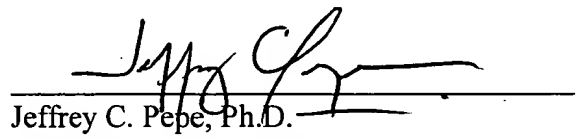
PATENT TRADEMARK OFFICE



Jeffrey C. Pepe, Ph.D.
Registration No. 46,985

JCP:lmp 276460

Phone: (206) 622-4900
Fax: (206) 682-6031

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph title beginning at line 15 of page 1 has been amended as follows:

-- Creation of Recombinant ~~Salmonella~~ *Salmonella* Strains --

Paragraph beginning at line 28 of page 12 has been amended as follows:

-- Several strains of *E. coli* produce fimbriae named curli, which are highly related to thin aggregative fimbriae from ~~Salmonella~~ *Salmonella* spp. Both TAF and curli are primarily composed of one major subunit protein, AgfA and CsgA, respectively. The primary sequence of AgfA and CsgA are 74% identical and 86% conserved [Collinson, 1996]; no other characterized fimbrial proteins in existing sequence databases have notable sequence similarity to either protein. Curli have also been extensively characterized [Bian, 1997; Hammar, 1995; Hammar, 1996; Olsén, 1993; Römling, 1998; Römling, 1998]; the operon encoding curli production has been sequenced and characterized in *E. coli* [Hammar, 1995] and was recently shown to be conserved (identity of 78%) in *Salmonella typhimurium* [Römling, 1998], which also produces thin aggregative fimbriae. This evidence indicates that thin aggregative fimbriae and curli are both members of the same distinct class of fimbriae. The gene for TAF, *agfA* (*csgA*) has been detected in 99.8% (603/604) of *Salmonella* isolates, but is less representative in other members of the *Enterobacteriaceae*, including only 19.0% (26/137) *E. coli* strains [Doran, 1993]. *agfA* is therefore genotypic of *Salmonella* spp. and occasionally found in *E. coli* and its subspecies, suggesting its origins were in *Salmonella* spp. and coopted into *E. coli.* --

Paragraph beginning at line 20 of page 18 has been amended as follows:

-- ~~Salmonella~~ *Salmonella* spp. are well developed vaccine vectors [Hackett, 1993]. Attenuated *Salmonella* strains can elicit protective immunity and induce secretory, humoral and cellular anti-*Salmonella* responses in hosts following oral immunization [Levine, 1996]. In addition, most ~~Salmonella~~ *Salmonella* spp. are facultative intracellular pathogens

[Fields, 1986] with a highly characterized invasion pathway [Galán, 1996] and can express antigens inside of host cells. These features, when combined with the ease of genetic manipulation in *Salmonella* spp., makes these facultative intracellular pathogens excellent candidates as vaccine vectors for the presentation of protective heterologous antigens [Curtiss III, 1994]. --

Paragraph beginning at line 23 of page 19 has been amended as follows:

-- Several methods of chromosomal gene replacement have been developed for the creation of ~~Salmonella~~ *Salmonella* vaccine vectors (discussed above). However, these methods insert the recombinant genes into the chromosome at non-native sites. As a consequence, expression of the recombinant genes would be predicted to be altered. There is a need for a method of chromosomal gene replacement in *Salmonella* to insert recombinant genes into native regions normally occupied by the wild-type genes. Two such methods exist for chromosomal gene replacements in *E. coli*. The method by Hamilton *et al.* (1989) relies on the use of a temperature sensitive pSC101-derived vector to perform the replacements. Gene replacement by this method does not leave (or add) any extraneous DNA elements and one drawback is having to cure final strains of freely replicating vectors. A more recent method proposed by Link *et al.* (1997) uses a vector related to the one used by Hamilton *et al.* (1989) with the addition of the *sacB* selectable marker to the vector to allow for selection for loss of the vector sequence upon gene replacement. --

Paragraph title beginning at line 11 of page 24 has been amended as follows:

-- Expression of Heterologous Epitopes in ~~Salmonella~~ *Salmonella* Flagella --